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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,023	06/28/2001	Vladmir R. Muzukantov	PENN-0749	7329

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/762,023	MUZUKANTOV ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 12/09/04, is acknowledged.

2. Claim 9 is pending and under examination.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

4. Claim 9 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Bowes et (Neurology 1995) in view of Mulligan et al (Amer. Pathol. 1993), or Panes (Amer. Physiol. 1995), and Muzykantov et al (BBA 1986), Runge et al or Torchilin et al (all of record).

Bowes *et al* teach that administration of an anti-lCAM-1 mAb and the drug tPA to rabbits prevents leukocyte adhesion and increases post ischemic duration at which thrombolytic therapy remains effective in cerebral ischemia and reperfusion (especially Abstract). Bowes *et al* also teach that administration of tPA alone improves neurologic outcome in models of ischemia, but that obstacles exist to therapy, and further that reperfusion may also result in additional neurologic damage as ischemic tissue is reoxygenated (abstract in particular).

The claimed invention differs from the Bowes *et al* teachings only by the recitation of conjugate and a non-internalizable antibody or ICAM-1 in claim 9.

Panes *et al* teach that ICAM-I is constitutively expressed on vascular endothelium of the rat and there are significant regional differences in magnitude of expression.

Mulligan *et al* teach anti-ICAM-1 mAb 1A29 accumulates in the pulmonary vasculature (see table I, and page 1744, 2nd col., 1st ¶ in particular), i.e., non-internalizable anti-ICAM-1 mAb 1A29, challenged with pro-inflammatory agents, and that blocking of ICAM-1 is tissue protective in a manner in which neutrophil recruitment is attenuated. Mulligan et al further

teaches that the radiolabeled anti-ICAM-1 (1A29) antibodies were intravenously injected (page 1741, under in vivo ICAM-1 quantification, in partricular).

Runge *et al* teach the thrombolytic drug tPA can be efficiently directed to the site of a thrombus by conjugation, i.e., chemical modification, to an anti-fibrin monoclonal antibody, resulting in both more potent and more selective thrombolysis (especially Abstract).

Torchilin *et al* teach that targeted accumulation of thrombolytic enzymes in the region of thrombus location can be achieved by their coimmobilization with specific antibodies (especially Abstract). Torchilin et al further teach drawbacks in administration of tPA alone include necessity of prolonged and continuous administration due to rapid physiologic inactivation far from the site of thrombolysis (especially page 322) may be resolved by the use of antibody-immobilized tPA.

Muzykantov *et al* teach targeting of fibrinolytic agents using antibody to regions of the vascular bed having an increased probability of clot formation.

The determination of the systematic administration of the conjugate is well within the purview of one of ordinary skill in the art at the time the invention was made and lends no patentable import to the claimed invention. The duration of treatment, the specific rout of administration and like factors within the knowledge and expertise of the medical practitioner. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Given the teachings of Mulligan *et al* that anti-ICAM-1 mAb 1A29 accumulates in the pulmonary vasculature, it would be immediately apparent to one skilled in the art that the antibody is non-internalizable.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate the tPA to a mAB (such as 1A29) as taught by Torchilin et al, Runge et al or Muzykantov *et al* targeting fibyrolytic agents or for other molecules recognizing mAb specific for target molecules on pulmonary vasculature of an animal using chemical modification as taught by Muzykantov et al or Runge et al and further, substitute the resultant conjugate for the anti-ICAM-1 mAb in the composition of Bowes et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because ICAM-1 is constitutively expressed on vascular endothelium as taught by Panes *et al.* or Mulligan et al and to prevent the deleterious side effects of administering tPA alone as taught by Torchilin et al or to more effectively target the tPA to regions of the vascular bed having an increased probability of clot formation as taught by Muzykantov et al.

Applicant' arguments submitted on 12/09/2004 have been considered but found not convincing.

Applicant submits that Bowes et al relate to methods for preventing neurologic damage occurring in the reperfusion phase of ischemic-reperfusion injury. Applicant points our the Bowes et al teachs that substantial evidence indicates that prevention of leukocyte adhesion improves neurologic outcome in animal models of stroke. Bowes et al examined the ability of monoclonal antibodies against ICAM-1 to prevent leukocyte adhesion to the vascular endothelium thereby reducing neurologic injury at breef postischemic delays and increase the postembolization interval at which thrombolysis was effective. Increased efficacy for TPA reported by Bowes is thus suggested to relate to the prevention of leukocytes adhesion by separate administration of anti-ICAM-1 antibody increasing the postischemic duration at which thrombolytic therapy remains effective. Applicant contends that there is nothing in this reference suggesting conjugation of the anti-ICAM-1 antibody to tPA. Applicant furhter points that the experiments of Bowes et al TPA was adminstered 2 hrs after administration of the anti-ICAM-1 antibody. Applicant points that timing of adminsitration is crucial for efficacy. Applicant submits that Bowes et al lacks of relevance to the instant claimed invention is also discussed in paragraph 5 of the Delaration by Dr. Muzykantov. Applicant argues that the secondary references fail to remdy the deficiencies in this primary reference as none teach a method for dissolution of fibrin clots in the pulmonary vasculature wherein the antibody-anti-thrombotic agent conjugate binds to the luminal surface of the pulmonary endothelium of the animal an dthe therapeutic action of the anti-thrombotic agent is localized in the blood compartment of the pulmonary vasculature. Applicant indicates that Runge et al directed a thrombolytic agent tPA to the site of a thrombus by conjugation of the tPA to an anti-fibrin monoclonal antibody and Torchilin teach targeted accumulation of thrombolytic enzymes in the regions of thrombus location. Applicant submits that Muzykantov et al do not teach targeting of fibrinolytic agents using antibody to regions of the vascular bed having an increased probability of clot formation but rather teach an anti-collagen antibody-erythrocyte-streptokinase complex designed to deliver fibrinolytics to the extravascular sub-indothelial interstitium, which is inaccessible for blood under normal and most pathological conditions (except rare conditions associated with overt disruption of the integrity of a blood vessel causing internal bleeding). Applicant submits that neither Runge et al, Torchilin or Muzykantov references teach a method for fibrin clot dissolution in the pulmonary vasculature wherein the antibody-anti-thrombotic agent conjugate is targeted not at the thrombus, but rather at the pulmonary vasculature.

However, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and not is it that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). See MPEP 2145.

Once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981). This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

The declaration by Vladimir Muzykantov under 37 CFR 1.132 filed 12/09/04 is insufficient to overcome the rejection of claim 9 based upon 35 U.S.C. § 103(a) as set forth in the last Office action because while Dr. Muzykantov strongly disagree with the Examiner's position that given Mulligan et al teachings that anti-ICAM-1 mAb 1A29 accumulates in the pulmonary vasculature, then it would be immediately apparent to one skilled in the art that the antibody is non-internalizable. Dr. Muzykantov points to a well-known paradigm that with most studied targets internalizaable antibodies show markedly **higher** accumulation vs non-internalizable ones. Dr. Muzykantov submits that accumulation in pulmonary vasculature, at the time of this invention (i.e. 1998) among all antibodies with characterized interanlizability, only internalizable one have been known to accumulate in the pulmonary vasculture. Specifically, anti-ICAM-1, represents a rare excption from this rule, but its internaliztion by endotheium had not been fully characterized until 2003. However, in 1995 Almenar-Queralt et at (Am J Pathol. 1995 Nov;147(5):1278-88), teach that kinetic binding studies of a ^{125}I-labeled monoclonal antibody to ICAM-1 revealed that approximately 8% of membrane ICAM-1 on the cytokine-activated endothelium was internalized in both coated and non-coated vesicles at 37°C, with a t1/2 of approximately 18 min and a rate of approximately 3200 molecules/minute (see abstract in particular). Therefore, it has been known prior to Applicant filing date that the accumulation of anti-ICAM-1 mAb 1A29 taught by in the pulmonary vasculature Mulligan et al is due to non-internalizable characteritic of the anti-ICAM-1 antibody. Such evidentiary reference supports the Examiner's position.

Applicant on page 10, 2nd paragraph of the response argues that references of Panes and Mulligan are silent with respect to any teaching whatsoever of a method for fibrin clot dissolution, conjugation of a therapeutic agent to an anti-ICAM antibody or binding of an anti-thrombtic agent to the luminal surface of the pulmonary endothelium of the animal via conjugation to an anti-ICAM antibody so that therapeutic action of the anti-thrombotic agent is localized in the blood compartment of the pulmonary vasculature.

Again, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller , 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc. , 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145. Further, the Runge *et al* reference has indicated a success in directing the thrombolytic drug tPA to the site of a thrombus by conjugation resulting in both more potent and more selective thrombolysis. Similarly, Muzykantov *et al* teach targeting of fibrinolytic agents using antibody to regions of the vascular bed having an increased probability of clot formation. Therefore, both Runge and Muzykantov reference teach the deficiency in Panes and Mulligan references.

Applicant on page 11 submits that the primary reference provides no suggestion or motivation, either in the combination of references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or combine the reference teachings to arrive at the instantly claimed method for fibrin clot dissolution. Further, Applicant submits that the combination of references provides no reasonable expectation of success with respect to the instantly claimed method for fibrin clot dissolution. Applicant further submits that the prior art references when combined neither teach or suggest all the claim limitations, namely a method or

fibrin clot dissolution in the pulmonary vasculature which involves administering non-internalizable antibody to ICAM-1 conjugated to an ant-thrombotic agent binds to the luminal surface of the pulmonary endothelium of the animal thus localizing the therapeutic action of the anti-thrombotic agent to the blood compartment of the pulmonary vasculature.

In contrast to applicant's assertions, there was clear teaching and therefore expectation of success to conjugate of the antibody to ICAM-1 to an anti-thrombotic agent as the claimed invention. Further, the references provide clear motivation to combine, wherein ICAM-1 is constitutively expressed on vascular endothelium as taught by Panes *et al.* or Mulligan et al and to prevent the deleterious side effects of administering tPA alone as taught by Torchilin et al or to more effectively target the tPA to regions of the vascular bed having an increased probability of clot formation as taught by Muzykantov et al.

5. No claim is allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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January 28, 2005

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